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ORINASE, DIABINESE AND DBI

A review of the studies of oral antidiabetic drugs published since The Medical Letter last discussed these drugs in 1959 (Medical Letter, 1:17 and 1:69) indicates that tolbutamide (Orinase — Upjohn) is still the drug of choice for most maturity-type diabetics who cannot be controlled by diet alone, but who can be adequately controlled with the oral agents. Chlorpropamide (Diabinese — Pfizer) is, however, effective in a small percentage of the patients who become refractory to Orinase. Phenformin (DBI — U.S. Vitamin), despite the frequency of its side effects, is occasionally useful as an adjunct to insulin in juvenile-type diabetics; it is also effective in some maturity-type diabetics who cannot be controlled with either Orinase or Diabinese or who have become refractory to these drugs.

TOXIC EFFECTS - The preference for Orinase over Diabinese where either can be used successfully is largely a matter of greater freedom from untoward effects with Orinase. As for DBI, if longer experience discloses no serious toxic effects, it will also be preferable to Diabinese for those patients who do not suffer gastrointestinal reactions. The claimed superiority of Diabinese over Orinase is related mainly to its greater duration of action, but the occasional occurrence of liver damage with Diabinese must be weighed against the convenience of its once-a-day dosage. Untoward reactions to Diabinese are much less frequent than they were when higher doses were commonly prescribed, but they are not absent with the limitation of dosage to 250 mg. daily (an amount roughly equivalent in effect to 1 Gm. of Orinase twice a day).

JUVENILE DIABETES - Unlike the sulfonylureas (Orinase and Diabinese), which act by stimulating insulin secretion, DBI appears to lower blood sugar by a direct effect on the metabolism of sugar within the cells, an effect which is independent of pancreatic activity. The drug can probably lower the blood sugar to some extent in all diabetics in whom the required doses can be tolerated. It rarely has sufficient effect, however, to control the juvenile-type unstable diabetic except during the early temporary remission of the disease which frequently follows initial treatment with insulin; with such diabetics, ultimate recourse to insulin is unavoidable, and the brief respite from insulin injections with DBI is gained at the risk of sudden and possibly fatal keto-acidosis.

Juvenile-type diabetics on DBI may develop ketosis without the appearance of sugar in the urine; acidosis may also occur during exercise as the result of ex-

cessive lactic acid accumulation. The manufacturer no longer recommends the use of DBI in juvenile-type diabetes except as an adjunct to insulin where it appears to have a stabilizing effect in some patients.

PLACE OF DBI - As already indicated, DBI has its greatest usefulness in stable, maturity-type diabetes where the patient cannot be controlled by diet alone, especially where neither Orinase nor Diabinese can be used successfully. DBI will be effective in some of these patients, though many will not be able to tolerate it. In some cases, the use of DBI along with either Orinase or Diabinese controls maturity-type diabetics resistant to any one of the drugs alone. The most frequent reactions to the drug — nausea, diarrhea, metallic taste and loss of appetite — are related to dosage.

Because it is still too early to rule out the possibility of serious long-term effects with any oral hypoglycemic agent, Medical Letter consultants feel that they should not be used in the patient who can be controlled by diet alone. In those who, for whatever reason, cannot be controlled by diet, Orinase (0.5 to 1 Gm. twice a day) should be tried. If there is reason to use Diabinese, the dose should be limited to 250 mg. daily. Dosage of DBI should start with not more than 25 mg. two or three times a day, with increases as necessary until adequate control is achieved or the patient shows intolerance to the drug.

Orinase costs the patient about 10¢ to 14¢ per 500-mg. tablet, or 40¢ to 56¢ for two grams daily. Diabinese costs about 13¢ to 17¢ for a 250-mg. tablet — the maximum recommended daily dose. DBI costs about 5¢ to 7¢ per 25-mg. tablet; dosage requirements vary widely and they are not related to the requirements for Orinase or Diabinese.

BACITRACIN

Bacitracin, USP has gained acceptance as an effective topical antibacterial agent for superficial skin infections, for local injection in surgical infections, and for instillation into body cavities infected by susceptible microorganisms. Its parenteral use for serious systemic infections has, however, been limited by the fear of renal injury. Some investigators believe the risk has been exaggerated, and that bacitracin should be administered more freely for systemic infections. In view of this belief, Medical Letter consultants and other authorities on antibiotic therapy were asked for their views.

LIMITATIONS OF USE - Most of those consulted would use parenteral bacitracin — with suitable precautions — for serious systemic infections caused by staphylococci resistant to penicillin G, tetracycline, erythromycin and novobiocin; but almost all of these would limit its use to patients who are allergic to methicillin (Staphcillin — Bristol; Dimocillin — Squibb), or in whom toxicity or bacterial resistance prevents successful use of vancomycin (Vancocin — Lilly) or ristocetin (Spontin — Abbott). Some would add kanamycin (Kantrex — Bristol) and neomycin to this list (despite their ototoxicity) on the ground that the largest usable dose of bacitracin is likely to be ineffective in severe staphylococcal infections.

INTRATHECAL AND TOPICAL USE - There was no difference of opinion among the consultants as to the usefulness of bacitracin when injected intrathecally to treat meningitis or neurosurgical infections caused by cocci sensitive to the antibiotic. Bacitracin has an antibacterial spectrum similar in many respects to that of penicillin. It is active against many cocci including streptococci, pneumococci and anaerobic cocci, in addition to some staphylococci. It is also active against clostridia of the gas gangrene group.

DOSAGE - The usual adult daily dose intrathecally is 10,000 to 20,000 units. In other localized surgical infections bacitracin may be injected directly into the local area or its periphery; it should be administered in doses of 1 to 5 cc. in a concentration of 1000 units per cc., together with an equal volume of 2% procaine. (Procaine should never be used intrathecally.) For superficial skin infections such as impetigo, it is a valuable topical agent, particularly when combined with neomycin, which has greater effectiveness against staphylococci.

In bacteremia caused by susceptible organisms, the adult dose range of bacitracin for parenteral use is from 15,000 to 25,000 units every six to eight hours administered intramuscularly, with the day's limit kept at 100,000 units (2 Gm.). If hematuria or persistent proteinuria occurs, or if the blood nitrogen shows a progressive rise, the drug should be stopped. Fluid intake and output should be carefully measured; bacitracin cannot be used safely when the urine output (in adults) is less than 800 cc. per day. Because bone-marrow damage is occasionally associated with the use of bacitracin, complete blood counts should be done twice weekly during therapy.

In summary, bacitracin is an effective and safe antibacterial agent for local and topical use in the treatment of coccal infections. Parenterally, it may be worth a cautious trial in patients with staphylococcal bacteremia where the organism shows in vitro sensitivity to bacitracin and is resistant to other oral or parenteral agents.

PHENISTIX AND PHENYLKETONURIA

Phenistix (Ames) is offered for use as a convenient "dip and read" test for phenylketonuria, a disease caused by a recessive genetic defect of phenylalanine metabolism. It occurs in about one in 20,000 infants and it leads to serious mental retardation when it is not detected and treated very early; despite the rarity of the disease, therefore, every infant should be tested for the presence of urinary phenylketone bodies, which usually appear by the third week of life. The earlier the phenylketone bodies are detected and treatment started, the better the chance of prevention of mental retardation. Treatment consists of the feeding of a diet with a very low content of phenylalanine; in such a diet, specially processed proteins are substituted for ordinary proteins.

FERRIC CHLORIDE TEST - In the usual office test for phenylketonuria, a drop of a 10% aqueous solution of ferric chloride is placed on a diaper freshly wet with urine; if the test is negative, the orange color of the ferric chloride persists; if positive, a blue-green or gray-green color appears within 30 seconds and fades rapidly thereafter. If the infant does not oblige with a wet diaper at the appropri-

ate time, the parent can be given a piece of filter paper and instructed to saturate it with the infant's urine, air dry it, and return it for testing. The presence of stool may interfere with the ferric chloride test, and numerous drugs, particularly phenothiazines and salicylates, may give color reactions; these are not, however, difficult to distinguish from the gray-green produced by phenylketonuria. Ferric chloride solution is inexpensive, sensitive, and stable for at least a year when stored in a plastic bottle (deteriorated solutions become cloudy).

Phenistix strips appear to be a satisfactory substitute for ferric chloride solution; whether they represent an improvement as claimed is questionable. The tips of the strips are impregnated with ferric ammonium sulfate and with magnesium salts and cyclohexylsulfamic acid to minimize potential interference by urinary phosphates and alkalinity. For the test, a strip is thoroughly wet with urine from a fluid sample or a wet diaper and compared after 30 seconds with a color scale. The manufacturer claims that Phenistix is superior to ferric chloride solution in avoiding false negative reactions due to interference by highly alkaline or high phosphate urine. Ten per cent ferric chloride solution (the recommended concentration) is sufficiently acid in itself, however, and high enough in ferric ions to be as reliable as Phenistix in these circumstances. If Phenistix is used, the manufacturer's directions should be carefully followed.

CHECK TESTS - In practice, 10% ferric chloride solution and Phenistix are equally sensitive and equally simple to use, and the color reactions produced by various drugs can be distinguished equally well with both. In any event, all positive or equivocal tests with either must be checked by laboratory determination of the fasting serum phenylalanine or by chromatographic study of the urine. The manufacturer states that Phenistix has been found useful as a guide to the adequacy of dietary management of phenylketonuria. Since good dietary management means keeping the serum phenylalanine levels below 5 mg. per hundred cc., and since phenylketonuria does not occur until the serum level reaches 12 mg. per hundred cc., neither Phenistix nor ferric chloride solution can substitute for laboratory determination of serum phenylalanine. Either test can, however, be used to detect gross departures from the prescribed diet.

POLIO VACCINE

The decision of the Surgeon General to license the production and marketing of Type I of the Sabin oral live-virus polio vaccine may prove to be an unfortunate one. The risk is that it will cause many people to forego the full series of injections of the Salk killed-virus vaccine, even though the new oral vaccine will not protect against paralytic poliomyelitis caused by types II and III. Type II is unimportant as a cause of infection, but type III now appears to be responsible for more cases of paralytic polio than type I, and there is some evidence of a further marked increase in the percentage of type III cases. Four injections of Salk vaccine at recommended intervals reduce the incidence of paralytic polio by close to 95 per cent, and physicians have an obligation to encourage the widest possible use of this vaccine in the coming months. The new oral vaccine should never be used as a substitute for a booster dose of Salk vaccine. If the physician wants to provide maximum protection for a child or an adult, he will accomplish much more with additional booster doses of killed-virus vaccine than with Type I oral vaccine.

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